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Safety, pharmacokinetics and pharmacodynamics of a novel anti-asthmatic drug, XC8, in healthy probands

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ABSTRACT

Introduction: XC8 (histamine glutarimide) is a novel agent which targets eosinophilic migration and mast cell degranulation and has shown anti-asthmatic effects in animal studies.
Objective: The objective of this placebo-controlled phase 1 study was to assess the safety of oral XC8 and to evaluate its pharmacokinetic and pharmacodynamic properties.
Methods: 32 healthy volunteers in three dose-escalation treatment groups (10 mg [n = 8], 50 mg [n = 8] and 200 mg [n = 16]) were randomized in a 3:1 ratio to XC8 or placebo respectively. The subjects received a single dose of the drug at Day 1 and then once-daily for 14 days (Days 8–21).
Results: No severe adverse events occurred. The number of adverse events was similar in the treatment arms compared to placebo and all subjects completed the study as planned. No clinically significant changes occurred in hematologic and biochemical blood tests in subjects receiving XC8. The pharmacokinetic data showed similar dose and time dependent mean plasma XC8 concentrations after single (Day 1) and multiple (Day 21) dosing. The mean maximum concentrations were 114–1993 ng/mL after single and 115–2089 ng/mL after multiple dosing. The mean times to maximum concentration were 0.68–1.01 and 0.67–0.98 h, respectively. There was no evidence for accumulation of XC8 after multiple dosing.
Conclusion: XC8 was safe and well tolerated. A phase 2 study is being performed to further evaluate the potential role of XC8 in asthma treatment.
Trial registration: ClinicalTrials.gov, NCT02882217.

1. Introduction

Asthma is a chronic, common and heterogeneous airway disease [1]. Asthma control is poor in more than 50% of patients and adherence to inhalation therapies is low [2–4]. Eosinophilic airway inflammation plays an integral part in the pathophysiology in all T2-high asthma phenotypes [5,6]. Peripheral blood eosinophils (PBE) correlate with airway inflammation, airway hyperresponsiveness and asthma severity and are routinely measured to assess eosinophilic airway inflammation [7–9].

XC8 (histamine glutarimide) is a novel anti-asthmatic agent which targets eosinophilic migration and mast cell degranulation by inhibition of maturation of chemokines (CCL2, CCL7, CCL8, CCL13). A previous study has shown that XC8 reduces airway resistance and eosinophil counts in bronchoalveolar lavage and lung tissue in sephadex induced lung inflammation in rats and ovalbumin induced asthma in guinea pigs [10].

This paper presents the results of a randomized, dose escalating, placebo-controlled multi-center, phase-1 study performed to assess the safety and tolerability of single and multiple doses of oral XC8 administered in healthy volunteers. The secondary endpoints were evaluating pharmacokinetic (PK) and pharmacodynamic (PD) properties after single and multiple dosing schedules.

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2. Methods

2.1. Study design

This was a randomized, placebo-controlled, dose-escalating, group-sequential phase 1 study designed to assess the safety, tolerability and PK of single and multiple doses of XC8 (http://clinicaltrials.gov identifier: NCT02882217). Subjects underwent a screening period of up to 14 days, during which their eligibility was assessed. Thirty-two healthy subjects were allocated to 3 dosing groups (10, 50, and 200 mg dosing) and randomized to treatment with XC8 or placebo in a 3:1 ratio (6 subjects receiving 10 and 50 mg XC8 and 2 placebo in treatment groups 1 and 2 and, and 12 subjects receiving 200 mg XC8 and 4 placebo in treatment group 3). Due to the dose escalating design (see 2.2 Study conduct) investigators and subjects were double-blinded regarding the randomization to active treatment and placebo, but not to the dosing group.

Men and women aged 18–50 years in generally good health and with a body mass index of 19–30 kg/m^2 were included. Female subjects of childbearing potential had to use a method of birth control with a failure rate of less than 1% per year. A full list of inclusion and exclusion criteria can be found in *E*-Supplement Tables 1 and 2

2.2. Study conduct

The study was conducted at two sites (Karl Landsteiner Institute for experimental and clinical pneumology, Vienna, Austria; Fraunhofer Institute for toxicology and experimental medicine [ITEM], Hannover, Germany). Informed consent forms and study protocol were reviewed and approved by the local ethics committees. Monitoring was performed by FGK Clinical Research GmbH, Munich, Germany. The study was conducted following local regulations, the Declaration of Helsinki and Good Clinical Practice guidelines.

Starting with the lowest dose treatment group, subjects received a single dose of XC8 or placebo on Day 1. After a wash-out period of 6 days, subjects received a once-daily dose for 14 subsequent days (Days 8–21). After safety data for all subjects in the treatment group were collected for at least 7 days (Day 29), a dose escalation committee reviewed clinical safety and safety laboratory data provided by the investigators and recommended further actions regarding the dose escalation of the next treatment group. If it was considered safe to proceed, the next higher dose level treatment group was treated following the same schedule as described for the lower dose level treatment group.

On Day 1 and Days 8–21, subjects had blood samples taken for PK analyses immediately before, and 20 and 40 min, and 1, 2, 4, 8, and 24 h after study drug administration. Follow-up visits were scheduled on Days 29 and 36. Further blood samples were taken on Days 1, 2, 8, and 22 to assess PBE. Safety assessments (safety laboratory, electrocardiogram and physical examination) were performed throughout the screening, single-dosing, multiple-dosing and follow-up period.

2.3. Investigational product

The investigational product was administered orally in the morning in film-coated tablets containing 10 or 100 mg of XC8. XC8 substance was produced and provided by FARMAK (Czech Republic). XC8 is a 1-(2-(1H-Imidazol-4-yl)ethyl)piperidine-2,6-dione based on IUPAC nomenclature. The investigational product was produced and released per current European Good Manufacturing Practice regulations. Study medication was stored below 25 °C and protected from light. To maintain the blind, XC8 and the placebo tablets had identical appearance, shape and color, as well as identical labeling and packaging.

2.4. Physical examination, vital signs and electrocardiogram

The physical examination included an assessment of the general appearance, skin, head, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, and nervous system. Vital signs (respiratory rate, heart rate, blood pressure, and body temperature) were measured in sitting position after the subject had rested for at least 5 min. Twelve-lead electrocardiogram was performed following standard procedures and evaluated locally at screening, Day 1 pre-dose and 8 h post-dose, Day 2, Day 8 pre-dose and Days 22, 29 and 36.

2.5. Laboratory evaluations

The safety laboratory examinations consisted of a complete blood count including leukocyte differential count, clinical chemistry including electrolytes, kidney function tests and liver function tests, and urinalysis. A complete list of all performed safety laboratory can be found in E-Supplement Table 3. The safety laboratory studies were performed immediately at the local study sites.

PK analysis was performed at Biopharm (Jilove u Prahy, Czech Republic) using a validated high-performance liquid chromatography tandem mass spectrometer method.

2.6. Data analysis

2.6.1. Baseline demographics

Baseline demographic data and medical history were summarized descriptively.

2.6.2. Safety analysis

The analysis of adverse events (AE) was focused on treatment emergent adverse events (TEAE), defined as AEs with onset after the first intake of study medication. Serious TEAEs and TEAE related to the study medication were listed separately. Pre-treatment-emergent AEs were listed, also. AEs were classified using system organ classes (SOC) and preferred terms (PT) as defined in the Medical Dictionary for Regulatory Activities (MedDRA®) version 19.0. MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Laboratory data, including hematology, clinical chemistry, and urinalysis data, were summarized by dose group and visit. Changes from Day 1 pre-dose to Day 2 and Day 8 pre-dose to later time points were presented using shift tables (employing the categories 'normal', 'abnormal, clinically not significant', and 'abnormal, clinically significant') and as absolute changes, if appropriate. Laboratory values were classified as abnormal if they were outside the local sites' laboratory reference ranges (see E-Supplement Table 3). In case of abnormal values investigators at the local site immediately assessed the change as either clinically significant or not. Any clinically significantly abnormal results were listed separately. Vital signs and body temperatures were summarized by visit. Results of physical examinations were listed. Shift Tables were used to present changes from Day 1 pre-dose to Day 2, and Day 8 pre-dose to any later time point using the categories 'normal', 'abnormal, not clinically significant', and 'abnormal, clinically significant'.

2.6.3. Pharmacokinetic data

Evaluated PK parameters were the area under the plasma concentration curve extrapolated to infinity (AUC_{inf}), area under the plasma concentration curve up to 24 h after the last study drug administration ($AUC_{0\text{-}24}$), area under the plasma concentration curve up to last sampling time with concentration above the limit of quantification ($AUC_{0\text{-}tlast}$), maximum serum concentration (C_{max}), last observed quantifiable concentration (C_{last}), median time to C_{max} (T_{max}), elimination half-life ($t_{1/2}$), elimination rate (K_{el}), average concentration over one dosing interval (C_{av}) and the accumulation ratio between Day 1 and Day 21 based on C_{max}, $AUC_{0\text{-}24}$, and AUC_{inf}. PK parameters were

calculated using non-compartmental analysis based on observed XC8 plasma concentrations and post-dose sampling times.

C_{max} and T_{max} were obtained directly from the measured concentrations. $AUC_{0\text{-}tlast}$ were calculated by the linear/log trapezoidal rule up to the last measured concentration above the lower limit of quantification. $AUC_{0\text{-}24}$ was calculated by the linear/log trapezoidal rule up to 24 h after study drug administration. C_{av} was computed as $AUC_{0\text{-}24/\tau}$, where τ was the dosing interval obtained from the post-dose time of the 24-h sample. K_{el} was estimated by log-linear regression on the apparent terminal elimination phase. AUC_{inf} was extrapolated to infinity as $AUC_{0\text{-}tlast} + C_{last}/K_{el}$. The elimination half-life was calculated as $t_{1/2} = \ln(2)/K_{el}$. The accumulation ratios were calculated based on C_{max}. The relationship between PK parameters and the nominal dose was explored assuming a power model ($PK = a \times Dose\ b$, which is equivalent to $\log[PK] = \log[a] + b \times \log[Dose]$). This relationship was evaluated for C_{max}, $AUC_{0\text{-}24}$ and AUC_{inf} after single (Day 1) and after multiple (Day 21) dosing. In line with the above equation, a linear regression was applied between the logarithm of the individual PK parameter and the logarithmic of the nominal dose. The dose-proportionality of PK parameters was assessed based on the slope (b in the above equation) estimate, with a slope significantly smaller or higher than 1 indicating an increase of the PK parameters lower or higher than expected from a dose-proportional relationship, respectively.

2.6.4. Pharmacodynamic data

Changes in PBE were summarized descriptively.

3. Results

3.1. Study population

All 32 screened subjects were randomized and received the study medication. In treatment groups 1 and 2, 6 subjects each received active treatment and 2 subjects each received placebo. In treatment group 3, 12 subjects received active treatment and 4 subjects received placebo. All 32 subjects completed the study as scheduled. Baseline demographic data are shown in Table 1. The median age was about 30 years, ranging from 20 to 50 years. Although the median age was markedly higher in the 50 mg XC8 treatment group (48 years), the range (31–50) was comparable to the other treatment groups and placebo. All subjects were Caucasian. All subjects took the study medication per randomization and per protocol.

3.2. Safety analysis

3.2.1. Adverse events

A summary of TEAEs is given in Table 2. 54% of subjects treated with XC8 and 75% of subjects treated with placebo experienced one or more TEAE(s). The number of TEAEs which were assessed to be related to the study medication by the investigators appeared to increase with increasing XC8 dose (1 report in 1 subject receiving 10 mg XC8, 4 reports in 3 subjects receiving 50 mg XC8, and 10 reports in 3 subjects treated with 200 mg XC8). None of the reported TEAEs were serious, led to premature termination, or resulted in death. One subject treated with 200 mg XC8 had experienced a pre-treatment-emergent event (upper respiratory tract infection). An overview of TEAEs by SOC and PT is provided in Table 3. No difference between active treatment and placebo or dose-dependency for XC8 was apparent. All TEAEs had resolved by Day 36.

3.2.2. Laboratory analysis

No shifts to clinically significantly abnormal values were observed in hematology. No subject in any of the XC8 treatment groups had shifts to clinically significantly abnormal values in the clinical chemistry laboratory. Two subjects treated with placebo had a shift from normal to clinically significantly abnormal values in the clinical chemistry laboratory (*see below*) and one subject in the 200 mg XC8 treatment group had clinically significantly abnormal urinalysis, which was later diagnosed as cystitis (assessed as not related to the study medication, *see below*).

One of the placebo-treated subjects had clinically significantly high values in both blood creatine phosphokinase and aspartate aminotransferase on Day 29, which were both reported as mild TEAEs with relation to the study medication. Blood creatine phosphokinase had increased from 56 U/L on Day 1 and from 55 U/L on Day 8–5095 U/L on Day 29. On all assessments before Day 29, values were within the normal range (≤168 U/L). The TEAE had resolved by Day 36. Similarly, aspartate aminotransferase levels had increased from 25 U/L on Day 1 and Day 8–126 U/L on Day 29. All assessments up until Day 29 were within the normal range (≤31 U/L). The TEAE had resolved by Day 36.

The other placebo-treated subject had an increase in the blood creatine phosphokinase on Day 8–726 U/L (Day 1: 191 U/L; normal range < 190 U/L), which was reported as moderate TEAE with no relation to the study medication. The subject had a further increase in creatine phosphokinase levels on Day 10–3268 U/L (1111 U/L in a repeated measurement); all these increases were assessed as not clinically significant. Creatine phosphokinase levels decreased to 347 U/L by Day 15 and the TEAE was considered resolved.

One subject in the 200 mg XC8 treatment group had clinically significant abnormal urinalysis values for nearly all urinalysis parameters from Day 15 onwards. Most of these parameters were already outside the normal range but not clinically significant on Day 8 pre-dose. The urinalysis parameters with a shift from normal or non-clinically significantly abnormal to clinically significantly abnormal for this subject after Day 15 included ketones, bilirubin, erythrocytes, leukocytes and

Table 1
Baseline demographics.

		Placebo (N = 8)	10 mg XC8 (N = 6)	50 mg XC8 (N = 6)	200 mg XC8 (N = 12)	Total (N = 32)
Sex						
Male	N (%)[a]	4 (50.0)	2 (33.3)	4 (66.7)	7 (58.3)	17 (53.1)
Female	N (%)[a]	4 (50.0)	4 (66.7)	2 (33.3)	5 (41.7)	15 (46.9)
Age [years]	Median	36.5	29.5	48.5	24.5	30.5
	Range	23–48	27–50	31–50	20–39	20–50
Weight [kg]	Median	81.2	86.6	77.5	78.0	80.6
	Range	65.0–109.0	59.6–97.9	62.9–83.5	60.0–97.0	59.6–109.0
Height [cm]	Median	176.0	180.0	176.0	174.5	177.5
	Range	159–192	167–185	163–187	163–204	159–204
BMI [kg/m^2]	Median	25.6	25.9	24.2	23.5	24.3
	Range	22.5–29.8	21.4–29.4	22.3–28.5	20.8–29.2	20.8–29.8

[a] Percentages are based on the total N in the analysis set. BMI = body mass index, N = number of subjects.

Table 2
Summary of TEAEs.

	Placebo (N = 8)	10 mg XC8 (N = 6)	50 mg XC8 (N = 6)	200 mg XC8 (N = 12)	Total (N = 32)
Number of TEAEs	13	4	11	14	42
Number (%)[a] of related TEAEs[b]	7 (53.8)	1 (25.0)	4 (36.4)	10 (71.4)	22 (52.4)
Number (%)[a] of subjects with TEAEs	6 (75.0)	3 (50.0)	4 (66.7)	6 (50.0)	19 (59.4)
Number (%)[a] of subjects with related TEAEs[b]	3 (37.5)	1 (16.7)	3 (50.0)	3 (25.0)	10 (31.3)

N = number of subjects, TEAE = treatment-emergent adverse event.
[a] Percentages are based on the number of events in each treatment group.
[b] Assessed as related to the study medication.

Table 3
TEAEs by SOC and PT.

SOC (MedDRA) *PT*	Number (%)[a] of subjects				
	Placebo (N = 8)	10 mg XC8 (N = 6)	50 mg XC8 (N = 6)	200 mg XC8 (N = 12)	Total (N = 32)
Gastrointestinal disorders	**1 (12.5)**	-	**1 (16.7)**	**1 (8.3)**	**3 (9.4)**
General disorders and administration site conditions	**1 (12.5)**	-	**1 (16.7)**	**2 (16.7)**	**4 (12.5)**
Infections and infestations	**2 (25.0)**	**1 (16.7)**	**2 (33.3)**	**4 (33.3)**	**9 (28.1)**
Nasopharyngitis	*2 (25.0)*	*1 (16.7)*	*2 (33.3)*	*1 (8.3)*	*6 (18.8)*
Investigations	**2 (25.0)**	-	-	-	**2 (6.3)**
Blood creatine phosphokiase increased-	*2 (25.0)*	-	-	-	*2 (6.3)*
Musculoskeletal and connective tissue disorders	-	**1 (16.7)**	**1 (16.7)**	-	**2 (6.3)**
Nervous system disorders	**2 (25.0)**	**1 (16.7)**	**3 (50.0)**	**1 (8.3)**	**7 (21.9)**
Headache	*2 (25.0)*	*1 (16.7)*	*3 (50.0)*	*1 (8.3)*	*7 (21.9)*
Respiratory, thoracic and mediastinal disorders	**2 (25.0)**	**1 (16.7)**	**1 (16.7)**	-	**4 (12.5)**
Total	**6 (75.0)**	**3 (50.0)**	**4 (66.7)**	**6 (50.0)**	**19 (59.4)**

Preferred terms are only displayed for TEAEs that were reported by ≥ 2 subjects in the same treatment group. N = 0 is shown as '-'.
MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.
[a] Percentages are based on the number of subjects in each treatment group.

bacteria. On Day 17, cystitis was reported that was assessed as not related to the study medication and may explain the abnormal urinalysis results described above.

E-Supplement Table 4 shows the changes from normal to not clinically significantly abnormal laboratory values.

3.2.3. Vital signs and electrocardiogram

No differences in vital signs were apparent between placebo and active treatment or between doses of XC8. No shifts to clinically significantly abnormal values were noted in the electrocardiogram.

3.2.4. Physical examination

In 4 subjects, abnormal findings were reported after intake of study medication. In the 10 mg XC8 group one subject had a discrete swelling of cervical lymph nodes (Day 36). In the 200 mg XC8 group one subject had a red throat as part of a viral infection (Day 8) and another subject had a left leg bruise from soccer (not related, Day 36). In the placebo group one subject had mild wheezes over the right chest (Day 22).

3.3. Pharmacokinetic data

The plasma concentration-time profiles for XC8 on Day 1 and Day 21 are shown in Fig. 1. The concentration time curves show a similar profile after single (Day 1) and multiple (Day 21) dosing. The exposure (AUC) and peak concentration (C_{max}) of XC8 showed an increase with increasing dose. The median time to C_{max} was 0.68–1.01 h after single dosing (Day 1) and 0.67–0.98 h after multiple dosing (Day 21).

The mean accumulation ratios on C_{max}, $AUC_{0\text{-}24}$, or AUC_{inf} were all close to 1 (0.88–1.15), suggesting no accumulation of XC8 after multiple dosing. The median elimination half-life increased with increasing dose from about 1.8 h on Day 1 in the 10 mg XC8 group to about 4.3 h on Day 1 in the 200 mg XC8 group but did not show major differences between multiple and single dosing. A summary of PK parameters for XC8 is shown in Table 4. The analysis of dose-proportionality is shown in Table 5. As indicated by slope at Day 1 included within the 95% CI, no significant departure from dose-proportionality was observed after single administration. After multiple dosing, a slight but significant ($p = 0.0058$) over-proportionality was observed for $AUC_{0\text{-}24}$. As the magnitude of the departure from dose-proportionality is very low (95% CI = 1.04–1.21), the over-proportionality is not expected to have any clinical relevance.

3.4. Pharmacodynamic data

No changes in PBE levels were apparent. Mean PBE levels stayed below 4% at all times for all treatment groups.

4. Discussion

XC8 was well tolerated and safe at doses of 10, 50, and 200 mg after single and multiple 14-day administration. No deaths occurred, no serious TEAEs were reported, and no TEAEs led to premature study termination. All reported TEAEs were mild or moderate and had resolved by Day 36. No apparent difference in TEAE frequency was observed between active dosing and placebo and no obvious dose-relationship for XC8 was seen. The number of subjects reporting related TEAEs appeared higher in the 200 mg XC8 dose group, which may be due to higher subject numbers in that dose group.

After oral administration, the drug was rapidly absorbed, and the median maximum concentration was reached after 0.68–1.01 h after single dosing. The median plasma elimination half-life of XC8 increased

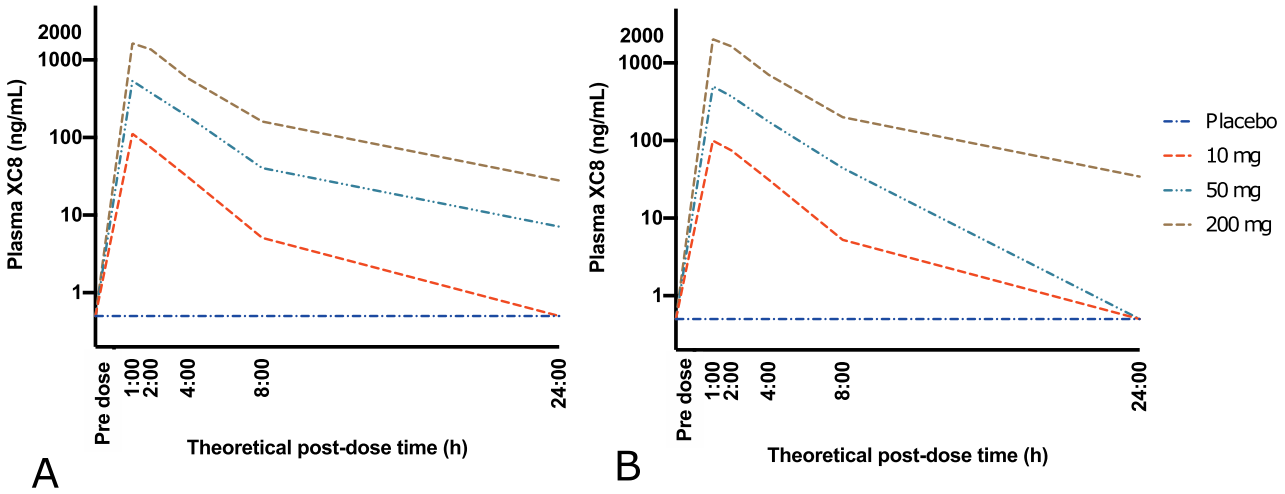

Fig. 1. Mean plasma concentration-time curves of XC8 after single dosing (Day 1, A) and multiple dosing (Day 21, B) of the study medication. Placebo: N = 8; 10 mg XC8: N = 6; 50 mg XC8: N = 6; 200 mg XC8 N = 12; N: number of subjects.

with increasing dose from 1.8 h in the 10 mg XC8 group to 4.3 h in the 200 mg XC8 group after single dosing. There was a slight over-proportionality after multiple dosing. This is not expected to be clinically relevant.

The main limitation of this study is that the subjects were healthy, non-asthmatic individuals. The bronchodilatory effect of XC8 demonstrated in animals needs to be confirmed in asthmatic individuals [10]. Similarly, the possible effect of XC8 on PBE should be reassessed in further studies with patients who are asthmatics and have elevated baseline levels of PBE. The PD data from this study cannot predict the mechanisms or effect of XC8 on patients with asthma. Furthermore, the results may not necessarily reflect the safety profile or PK in other ethnicities as all subjects were Caucasian.

The majority of pharmacological interventions recommended as controller therapy for adult mild and moderate asthmatic patients are administered via inhaler [1]. Inhalation therapies in asthma generally have a very beneficial safety profile [11,12]. However, despite educational tools seeking to improve inhaler adherence, it remains low [13]. An orally administered anti-asthmatic drug with an adequate safety profile could be a viable alternative for some patient groups.

XC8 was well tolerated and safe in healthy volunteers. Studies investigating XC8 in asthmatic patients are currently being performed.

Table 4
Summary of Pharmacokinetic data for XC8.

Geometric mean (CV [%])				
Parameter	Day	10 mg XC8 (N = 6)	50 mg XC8 (N = 6)	200 mg XC8 (N = 12)
$AUC_{0\text{-}24}$ [h·ng/mL]	1	290 (42.5)	1929 (26.9)	7013 (26.2) b
	21	284 (25.1)	1674 (31.9) c	8228 (21.7)
$AUC_{0\text{-}tlast}$ [h·ng/mL]	1	290 (42.5)	1929 (26.9)	6461 (29.4)
	21	284 (25.1)	1818 (35.5)	8228 (21.7)
AUC_{inf} [h·ng/mL]	1	407 (12.9) a	1706 (8.3) a	6324 (28.4) d
	21	344 (8.7) b	1815 (37.6) b	7729 (17.3) d
C_{max} [ng/mL]	1	114 (25.5)	626 (20.2)	1993 (26.3)
	21	115 (20.9)	552 (30.6)	2089 (17.7)
C_{av} [ng/mL]	21/1	11.8 (25.1)	69.8 (31.9) c	343 (21.8)
$R_{AUC0\text{-}24}$	21/1	0.98 (24.9)	0.92 (10.0) c	1.14 (14.3) b
R_{AUCinf}	21/1	0.88 (21.4) b	NE d	1.15 (17.2) e
R_{Cmax}	21/1	1.01 (8.7)	0.88 (28.1)	0.99 (20.1)
Median (range)				
$t_{1/2}$ [h]	1	1.78 (1.56–2.07) a	1.86 (1.59–3.79) a	4.26 (3.86–6.43) d
	21	1.66 (1.24–2.23) b	1.89 (1.76–4.89) b	4.55 (3.08–6.15) d
t_{max} [h]	1	0.83 (0.67–1.00)	0.68 (0.33–1.00)	1.01 (0.67–2.02)
	21	0.82 (0.33–2.00)	0.67 (0.32–2.03)	0.98 (0.33–2.00) c
K_{el} [1/h]	1	0.39 (0.34–0.44) a	0.37 (0.18–0.44) a	0.16 (0.11–0.18) d
	21	0.42 (0.31–0.56) b	0.37 (0.14–0.39) b	0.15 (0.11–0.23) d

As all data in the placebo group are NE or zero, the group is not shown.
$AUC_{0\text{-}24}$ = area under the plasma concentration curve up to 24 h after the last study drug administration, $AUC_{0\text{-}tlast}$ = area under the plasma concentration curve up to last sampling time with concentration above the limit of quantification, AUC_{inf} = area under the plasma concentration curve extrapolated to infinity, C_{av} = average concentration over one dosing interval, C_{max} = maximum plasma concentration, CV = coefficient of variation, K_{el} = elimination rate, N = number of subjects, NE = not estimable, R = accumulation ratio, SD = standard deviation, $t_{1/2}$ = elimination half-life, t_{max} = time to C_{max}.
a N = 2 missing. b N = 3 missing. c N = 1 missing. d N = 4 missing. e N = 6 missing.

Table 5
Analyisis of dose-proportionality of PK parameters.

Parameter	Day	Slope estimate	95% CI
$AUC_{0\text{-}24}$ [h·ng/mL]	1	1.06	0.94, 1.17
	21	**1.12***	**1.04, 1.21**
AUC_{inf} [h·ng/mL]	1	0.92	0.83, 1.01
	21	1.04	0.94, 1.14
C_{max} [ng/mL]	1	0.95	0.86, 1.03
	21	0.97	0.89, 1.04

*: after multiple dosing, a slight but statistically significant ($p = 0.0058$) over-proportionality was observed for $AUC_{0\text{-}24}$. $AUC_{0\text{-}24}$ = area under the plasma concentration curve up to 24 h after the last study drug administration, AUC_{inf} = area under the plasma concentration curve extrapolated to infinity, CI = confidence interval, C_{max} = maximum plasma concentration, PK = pharmacokinetic.

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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pupt.2019.101852.

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